EP-1199

The identification of putative biomarkers of radioresistance in rectal cancer tissue using antibody microarray

B. Onal[1], L. Bowden[1], S. Seedat[1], S. Maher[2], I.A. Hunter[3], L. Cawkwell[1]

[1]*University of Hull, Cancer Biology Proteomics Group, Hull, United Kingdom*

[2]*University of Hull, School of Biological Biomedical and Environmental Sciences, Hull, United Kingdom*

[3]*Castle Hill Hospital, Academic Surgical Unit, Hull, United Kingdom*

Purpose/Objective: Despite significant research input aiming to improve therapy regimens, rectal cancer remains as one of the cancers with significant morbidity rates. Radiotherapy has been shown to lower 10-year local recurrence by approximately 50%. A substantial number of rectal tumours fail to respond to radiotherapy which not only presents a barrier for effective cancer treatment bu also means that those patients with therapy resistant tumours endure the harmful side effects of radiotherapy for no therapeutic gain. Therefore, it is important to identify biomarkers capable of predicting a tumour's response to radiotherapy prior to treatment which can improve therapy outcomes. The aim of this study is to identify putative protein biomarkers of radiotherapy resistance using rectal cancer tissue biopsy samples by employing comparative proteomic tools. Ultimate aim is to translate these biomarkers into an assay panel for routine cancer screening aiding the personalisation of cancer treatment.

Materials and Methods: Following ethical approval (Sheffield REC ref 10/H1308/37), two pairs of pre-treatment rectal cancer biopsy samples (radioresistant versus radiosensitive) were investigated using antibody microarray to identify differentially expressed proteins (DEPs) involved in mediating radiotherapy resistance. Data obtained from the experiments were subjected to data mining using Ingenuity Pathway Analysis (IPA) which mapped these DEPs onto their most relevant canonical signalling pathways.

Results: The antibody microarray analysis of the clinical samples revealed 25 DEPs and 46 DEPs from the first and the second experiment, respectively. The IPA analysis of these combined generated 253 canonical pathways. Amongst these, the most interesting pathways included p53 signalling (12 DEPs mapped), death receptor signalling (7 DEPs mapped), apoptosis signalling (5 DEPs mapped) and EGF signalling (4 DEPs mapped). Radiotherapy is known to initiate cellular apoptosis via the intrinsic (mitochondrial) apoptotic pathway. However, the identification of some regulatory proteins involved in the extrinsic pathway (death receptor) apoptotic pathway (**Figure 1**) has revealed a potential link between radiotherapy and this pathway.

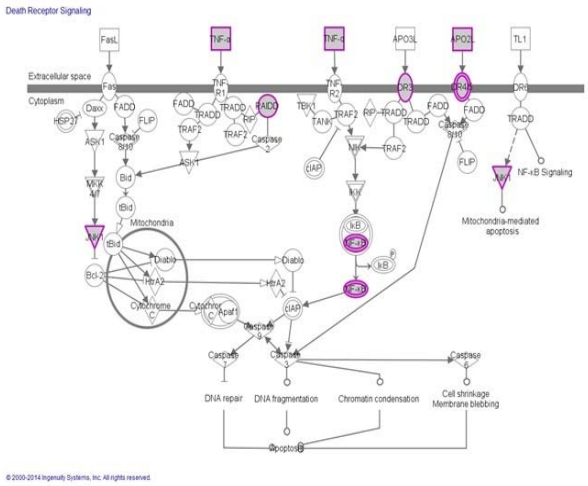

Figure 1: Death Receptor Signalling

A total of 7 DEPs were mapped onto the Death Receptor Signalling pathway, namely CRADD, TNFRSF25, MAPK8, TNFSF10, NFKB1, TNFRSF10A and TNF.

Conclusions: Antibody microarray analysis of rectal cancer biopsy samples has enabled the identification of a number of DEPs which may be involved in mediating response to radiotherapy. However, further confirmation with western blotting and validation with immunohistochemistry are required before such biomarkers can be introduced into routine clinical management of cancer patients.

EP-1200

Validation of a rectal cancer outcome prediction model in routine Chinese patients

L. Shen[1], J. Van Soest[2], J. Wang[1], J. Yu[3], W. Hu[1], Y.U.T. Gong[3], V. Valentini[4], Y. Xiao[3], A. Dekker[2], Z. Zhang[1]

[1]*Shanghai Medical College Fudan University, Radiation Oncology Department, Shanghai, China*

[2]*GROW School for Oncology and Developmental Biology Maastricht University Medical Centre, Radiation Oncology Department, Maastricht, The Netherlands*

[3]*Jefferson Medical College of Thomas Jefferson University, Radiation Oncology Department, Philadelphia, USA*

[4]*Università Cattolica del Sacro Cuore, Radiation Oncology Department, Rome, Italy*

Purpose/Objective: The risk of local recurrence, metastases and overall survival of locally advanced rectal cancer after preoperative chemoradiation and curative surgery can be estimated by prediction models and visualized using nomograms, which have been trained and validated in European clinical trial populations. This study aims to validate these prediction models in a routine clinical Chinese cohort.

Materials and Methods: From 2006 to 2012, clinical data of 277 consecutive locally advanced rectal adenocarcinoma patients treated with preoperative chemoradiation and curative surgery from a single Chinese Cancer Center, were retrospectively collected and used for external validation. Concordance index (C-index) and calibration curves were used to assess the performance of the previously developed

prediction models in this routine clinical validation population.
Results: The C-index for the published prediction models was 0.72, 0.75 and 0.72 in predicting 2-year local recurrence (LR), distant metastases (DM) and overall survival (OS) in the Chinese population, respectively. Kaplan-Meier curves indicated good discriminating performance of local control, however, couldn't discriminate a low-risk and medium-risk group well for distant control and overall survival. Calibration curves showed a trend of underestimation of local and distant control, as well as overall survival in the observed data compared with the model predicted one.
Conclusions: We externally validated three models for predicting 2-year LR, DM and OS of locally advanced rectal cancer patients who underwent preoperative chemoradiation and curative surgery with good discrimination in a single Chinese cohort, however the model overestimated the local control rate compared to observations in the clinical cohort. Furthermore, validation in other clinical routine cohorts and optimization of the prediction model including additional prognostic factors will enhance model validity and enhance applicability for personalized treatment of locally advanced rectal cancer.

EP-1201

Initial response of hepatic cancer treated with dynamic tumor-tracking stereotactic body radiotherapy

M. Kokubo[1], K. Takayama[2], H. Tei[3], Y. Iizuka[4], T. Imagumbai[1], Y. Kosaka[1], N. Ueki[4], Y. Suginoshita[3], T. Inokuma[3], M. Hiraoka[4]
[1]*Kobe City Medical Center General Hospital, Department of Radiation Oncology, Kobe, Japan*
[2]*Institute of Biomedical Research and Innovation, Division of Radiation Oncology, Kobe, Japan*
[3]*Kobe City Medical Center General Hospital, Department of Gastroenterology, Kobe, Japan*
[4]*Kyoto University Graduate School of Medicine, Department of Radiation Oncology and Image-applied Therapy, Kyoto, Japan*

Purpose/Objective: This study is to report initial clinical response of hepatocellular carcinoma (HCC) treated with dynamic tumor-tracking stereotactic body radiotherapy (DTT-SBRT) with real-time monitoring using the Vero4DRT system.
Materials and Methods: Eligibility criteria for this study were (1) one liver tumor with a diameter of 50mm or less, (2) technical difficulties for ablation therapies, inoperable, (3) performance status of 0-2, (4) Child-Pugh score of 8 or less, and (5) respiratory motion of 10mm or more. A fiducial marker (Visicoil) was placed near the tumor percutaneously under ultrasonographic guidance in advance. Internal target volume (ITV) for tracking was defined on the end-exhale phase of a 4DCT set. The ITV was delineated to compensate tumor-marker variation during respiration. Planning target volume (PTV) margin was defined for each patient taking some factors into account: interfraction variation of positions between the tumor and Visicoil, 4D modeling error, baseline drift of the abdominal wall movement, and mechanical error of the Vero4DRT.
Between August 2013 and August 2014, nine patients were included in this study. Three were male and six were female. A median age was 79 years old with the range from 68 to 88. A median tumor diameter was 30 mm with the range from 8 mm to 50 mm. In the Child-Pugh classification, five patients were classified to the Child-Pugh A, and others were classifies to B. Six patients were treated with 48 Gy in four fractions and others with tumor near digestive tract were treated with 56 Gy in eight fractions at isocenter by using 6-MV photon beam.
Results: DTT-SBRT was performed successfully. In contrast-enhancement CT or MRI after 3 months or more from DTT-SBRT, early arterial enhancement of HCC disappeared in eight patients. The other one had still early arterial enhancement in the tumor but this enhancement area was decreased at 45 days later from DTT-SBRT. All patients were classified to the same Child-Pugh criteria. No grade 2 or more adverse effect was noted. Two patients had a new HCC outside irradiation field.
Conclusions: DTT-SBRT with real-time monitoring using Vero4DRT system seemed to be effective in the treatment of HCC. DTT-SBRT has the possibility of alternative method in the treatment of HCC.

EP-1202

Outcomes of adjuvant chemoradiotherapy following local excision for patients diagnosed as early rectal cancer

N. Taek-Keun[1], Y. Mee Sun[1], S. Ju-Young[1], A. Sung-Ja[1], C. Woong-Ki[1], K. Yong-Hyeob[1], J. Jae-UK[1]
[1]*Chonnam Natioanl University Medical School, Radiation oncology, Kwangju, Korea Republic of*

Purpose/Objective: We evaluated the outcomes of adjuvant chemoradiotherapy (CRT) following local excision in patients diagnosed as early rectal cancer.
Materials and Methods: Eighty five patients who had completed postoperative adjuvant CRT after local excision of early rectal cancer were included in this analysis. All patients were pathologically confirmed as stage T1 or stage T2 rectal cancer after local excision. The radiation dose ranged from 39.6 Gy ~ 59.4 Gy (median; 50.4), given in 1.8 Gy fractions over 4 or 7 weeks. A concurrent chemotherapy regimen of fluorouracil (425 mg/m^2/day) and leucovorin (20 mg/m^2/day) was administered for 4 days during week 1 and 5 of radiotherapy except 2 patients (2.4 %) who refused chemotherapy.
Results: Seventeen patients (20 %) showed pathologic stage T2 and 20 patients (23.5 %) showed resection margin of less than 3 mm. The median duration of follow-up was 49 months. The median survival was not reached. The 5-year overall survival, locoregional relapse-free survival, and disease-free survival rate for all 85 patients were 96.8 %, 92.3 %, and 91.3 %, respectively. The patients with pathologic T2 stage (p = 0.004) or resection margin < 3 mm (p = 0.006) showed worse disease-free survival in multivariate analysis. In thirty-four patients with pathologic T2 stage and/or resection margin < 3 mm, four patients who received radiotherapy of 54.0 Gy did not develop any recurrence, while 3 out of 30 patients (10.0 %) of equal or less than 50.4 Gy developed local failure.
Conclusions: Postoperative CRT following local excision in patients with early rectal cancer could be effective adjuvant treatment without revision radical surgery. However, we recommend that radiotherapy dose of 54.0 Gy might be necessary to achieve better local control in the patients with pathologic T2 stage and/or resection margin < 3 mm.